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DRUG BULLETIN

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Antipsychotic Switching: When, How, Why?

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There are currently no definitive antipsychotic switching guidelines, however, certain strategies may be more appropriate in individual cases(1). This bulletin will review the reasons for switching, evaluate various switching methods and recommend switching strategies for individual antipsychotic agents.

Switching Rationale

Why switch antipsychotics? (2)

- Persistent positive or negative symptoms
- Intolerable adverse effects
- Partial or non-compliance (for switches to depots)
- Patient preference

Situations where switching should be reconsidered:

- Avoid switches for patients who have recently recovered from a psychotic episode for 3 to 6 months(3).
- Patients that are compliant on a depot preparation with a history of oral non-compliance should not be switched to oral medication for at least one year(3).
- Switching between antipsychotics is not indicated if an exacerbation of symptoms represents an unacceptable risk to the patient or others(7).
- Compliance should be assessed before switching due to lack of efficacy(3).

Switching Strategies

Table 1 details the advantages and disadvantages of four switching paradigms.

The potential problems of switching antipsychotics include; discontinuation syndromes, changes in psychopathology, pharmacodynamic interactions, pharmacokinetic interactions and neuroleptic malignant syndrome and (8). All medication switches should include appropriate monitoring for these effects.

A recent systematic review with meta-analysis suggests that there is no evidence that gradual discontinuation and replacement is safer or more effective than abrupt change(9). However, the drug properties of both antipsychotics involved in

Table 1: Antipsychotic switching strategies(3, 4)

	Method	Advantages	Disadvantages
1	Withdraw the first drug gradually and begin the second drug following a wash-out period	Lowest interaction potential Side-effects of the second drug are less likely to be confused with withdrawal effects of the first drug(5)	Risk of relapse Not feasible if patient is symptomatic
2	Stop the first drug immediately and commence the second drug at usual starting dose, increasing gradually	Low interaction potential Required when the patient has had a serious adverse effect to the first drug e.g. blood dyscrasias with clozapine	Risk of withdrawal effects Risk of relapse Requires close supervision
3	Cross titration: Over 2-4 weeks, gradually decrease the first drug, whilst starting the second drug at a low dose and gradually increasing dose	In general, the preferred method(6) Useful for switches from high potency antipsychotics to low potency antipsychotics Useful for switches where cholinergic rebound may occur	Risk of additive adverse effects and interactions If taper is too quick, both drugs may be given at sub-therapeutic doses Risk of medication errors
4	Overlap: Maintain first drug at usual dose for 2-3 weeks, initiate and up-titrate second drug to therapeutic dose, then gradually withdraw the first drug over 1-2 weeks	Suitable if relapse prevention is of greatest concern Most appropriate if the patient has recently recovered from acute relapse with the first drug	Risk of additive adverse effects and interactions Potential risk of continued polypharmacy Risk of medication errors

the switch should be considered in each case(10). Aside from drug property considerations, individual patient factors should be considered before switching. Special populations such as the elderly, neuroleptic naive, or those with renal or hepatic impairment may require a slow titration/switching strategy(8, 11).

Discontinuing the First Antipsychotic

The potential problems of discontinuing the first antipsychotic during a medication switch include discontinuation effects and psychotic relapse. Table 2 from Weiden et al lists the common withdrawal syndromes that can occur during antipsychotic or anticholinegic discontinuation.

Table 2: Antipsychotic discontinuation effects(3)

Category	Description	Timing	Comments
Anticholinergic withdrawal/ Cholinergic rebound	Malaise, nausea, vomiting, diarrhoea	First few days	Occurs with rapid withdrawal of antipsychotics with anticholinergic activity, or for switches to less anticholinergic antipsychotics. Can be managed with anticholinergics
Rebound akathisia	Symptoms of akathisia but often indistinguishable from psychosis or anxiety	First few days	Occurs with antipsychotic or anticholinergic withdrawal Use of propranalol, cyproheptadine, benzodiazepines or clonidine may be used to treat akathisia(12)
Rebound parkinsonism	Parkinsonian symptoms of tremor, muscle rigidity and akinesia	First week	Occurs when an anticholinergic is discontinued at the same time as a high-potency antipsychotic May also occur after discontinuing low-potency antipsychotics
Withdrawal dyskinesia	Choreoathetoid movements that are indistinguishable from tardive dyskinesia	1 to 4 weeks May take up to 6 months to abate	Most likely to occur when switching from an antipsychotic with a high D_2 affinity to low D_2 affinity(13) A slow down-titration can minimize risk(13)

When discontinuing antipsychotics with significant anticholinergic activity, a slow taper strategy is recommended (3). If anticholinergic medications were used to treat EPSE before a switch, these should be discontinued over a three week period after the first antipsychotic has been discontinued to prevent rebound parkinsonism and rebound anticholinergic effects(2).

In addition to withdrawal effects, relapse or destabilization may occur after abrupt discontinuation of an antipsychotic(14, 15). The proportion of patients relapsing per month may be threefold greater after abrupt discontinuation of treatment compared to a gradual reduction in dose (reduction over two weeks to two months)(16). In particular, rapid withdrawal of drugs that are loosely bound to the D_2 receptor, such as clozapine and quetiapine are associated with a high incidence of rebound psychosis(11, 16).

Commencing the Second Antipsychotic

The relative pharmacokinetic and pharmacodynamic properties of the two antipsychotics will influence the choice of switch strategy.

Switch strategies 3 and 4 may be associated with higher rates of adverse effects, especially when the adverse effects are shared between the two antipsychotics. In particular, the adverse effects of sedation, orthostatic hypotension, EPSE, prolactin elevation, lowered seizure threshold and QT interval prolongation may be worsened. Hence, a washout period may be required in cases where there is an additive adverse effect burden. This may be necessary for switches in high-risk patients involving drugs with marked effects on the QT interval(17). In contrast, switch strategy 3 or 4 may be suitable where gradual dose escalations are required for the second antipsychotic. This is necessary for antipsychotics with orthostatic effects or for high potency drugs that can induce EPSE (5, 18).

Problems may also occur where there are significant differences between the properties of the two drugs. Rebound insomnia may occur when switching from a sedating antipsychotic to a less-sedating antipsychotic(19). Rebound insomnia may require management with short-term benzodiazepine use(19). As mentioned earlier, discontinuation effects may be more pronounced during switches to antipsychotics with different affinities for D_2 or cholinergic receptors.

The potential for pharmacokinetic interactions should also be considered when two antipsychotics are used concurrently. Cytochrome P450 isoenzymes are involved in the metabolism of many antipsychotics. Caution is required when cross-tapering antipsychotics eliminated by the same cytochrome subsystem(7).

The risk of neuroleptic malignant syndrome (NMS) is present during any switch between

antipsychotics. NMS is characterized by autonomic instability, EPSE, hyperpyrexia and altered mental state. A sudden blockade of D_2 receptors is considered to be a contributing factor in NMS(20). In 66% of cases, NMS occurs within two weeks of initiation or change in antipsychotic treatment(20).

Post-switching Considerations

- The first antipsychotic should be ceased within three months of commencing any cross-titration(24).
- Target symptom response should be assessed after 3-6 weeks for an acute psychotic episode, or after 3 months for stable patients following complete antipsychotic switch(24).
- Women treated with conventional antipsychotics, risperidone or amisulpride often experience amenorrhoea and galactorrhoea. Normalization of prolactin levels following medication change leads to return of menses and fertility after about 3 months(24).

Specific Medication Switches

Table 3 compares drug properties of antipsychotics that may influence the choice of switching method. A brief discussion on specific switching strategies for various antipsychotics is included here.

Typical Antipsychotics

Typical Oral Antipsychotics

Chlorpromazine dose equivalents can be used to determine an equivalent dose for switching between typical antipsychotics(5). When switching from a low potency antipsychotic to high potency antipsychotic, the first drug should be slowly discontinued to prevent cholinergic rebound(11). Switch strategy 3 or 4 is recommended when switching from a typical antipsychotic to an atypical antipsychotic, as a gradual onset of action may occur with some atypicals(11). When switching from an atypical antipsychotic to a typical antipsychotic, a slow discontinuation of the atypical is recommended to minimize risk of rebound psychosis(11).

Typical Depot Antipsychotics

It may take several months for a depot preparation to reach steady state. During this time, interim oral supplementation may be required(25). The time to steady state for the typical depots:

- Flupenthixol decanoate, 10-12 weeks;
- Fluphenazine decanoate, 6-12 weeks;
- Haloperidol decanoate, 10-12 weeks;
- Zuclopenthixol decanoate, 10-12 weeks(5).

Direct switches from one typical depot to another can often be made uneventfully(5).

For switches from a depot to oral antipsychotic, a one month cross-titration taper has been shown to be effective and safe(2).

Atypical Antipsychotics

Risperidone long-acting injection (RLAI)

It takes 3-4 weeks for the first RLAI to produce therapeutic plasma levels(17). Patients must be maintained on a full dose of their previous oral antipsychotic for at least three weeks after the administration of the first injection(12).

If changing from a conventional depot, give RLAI one week before the last depot injection is given or in place of the last depot injection(12, 26). In general, the starting dose of RLAI should be 25mg every two weeks(12). The dose of RLAI should not be increased until after the patient has

Table 3: Relative Effects of Antipsychotics (5, 8, 12, 21-23)

	D_2 affinity	Anticholinergic	Extrapyramidal	Hypotension	Cardiac	Sedation	Proconvulsant
Chlorpromazine	++	+++	++	+++	++	+++	+++
Flupenthixol	++	++	++	+	+	+	++
Fluphenazine	+++	++	+++	+	++	+	++
Haloperidol	+++	+	+++	+	+++	+	0/+
Pericyazine	++	+	++	+	++	+++	++
Thioridazine	++	+++	+	+++	+++	+++	++
Trifluoperazine	+++	+	+++	+	++	+	0/+
Zuclopenthixol	+++	++	++	+	+	++	+
Amisulpride	++	+	+	0	++	0	+
Aripiprazole	+	0	0/+	0	0	0	+
Clozapine	+	+++	0	+++	+++	+++	+++
Olanzapine	++	+	0/+	+	+	+	++
Quetiapine	+	+	0	++	+	+++	+
Risperidone	++	+	+	+++	+	++	+

Effect: 0, absent/very low; +, low; ++, moderate; +++, high.

been on a dose for four weeks(17).
Patients who have stabilized on a high dose of conventional depot may require a starting dose of 37.5-50mg(12).
The last dose of RLAI will stop releasing risperidone six weeks later, any new drug should be introduced at this stage(5).

Amisulpride

Switching strategies 2 or 3 are suitable for amisulpride(17, 27). If a cross-titration approach is used, the first antipsychotic should be reduced over 1-4 weeks(27). A starting dose of 100-300mg is recommended if negative symptoms predominate or in the case of relapse due to non-compliance, a starting dose of up to 800mg can be used(27).

Aripiprazole

Aripiprazole can be switched to by: 1) immediate initiation of 30mg/day with simultaneous immediate discontinuation of current antipsychotic; 2) immediate initiation of 30mg/day of aripiprazole while tapering current antipsychotic over two week; or 3) up-titrating aripiprazole to 30mg/day over two weeks, while simultaneously tapering off current antipsychotic (17, 28).
There have been case reports of worsening of psychosis during switches to aripiprazole(29). Aripiprazole functions as a weak partial agonist at the postsynaptic D_2 receptor in hypodopaminergic states and as an antagonist when dopaminergic activity is increased. Psychosis may be worsened during a switch by the combination of a large post-synaptic D_2 receptor availability and a hypodopaminergic state following discontinuation of the first antipsychotic combined with the D_2 agonist action of aripiprazole(29). Nausea, vomiting and initial restlessness have also been reported when aripiprazole has been initiated at full doses(18).

Clozapine

When switching from a previous antipsychotic to clozapine, switch strategy 1 is recommended(17). The first antipsychotic should be tapered down over one week. Once the first antipsychotic has been discontinued for 24 hours, clozapine can be commenced at a dose of 12.5mg and tapered up to therapeutic levels over 2 weeks(17). If prior discontinuation of the first antipsychotic is not a realistic option, combination therapy can be used with caution during the transition period. The dose of the first antipsychotic should be tapered down over a week, while gradually tapering the clozapine dose up (17). Particular caution is required when switching from a drug that is known to be myelosupressive or that can reduce the seizure threshold, as these effects may be additive with clozapine(30).

Olanzapine

When switching from a conventional antipsychotic or risperidone to olanzapine, the most effective strategy is to add a therapeutic dose of olanzapine (up to 10mg/day) while gradually discontinuing prior medication over two weeks(31). Although clozapine and olanzapine have similar affinities for muscarinic receptor subtypes, cholinergic rebound has been described with a rapid switch from clozapine to olanzapine(32).

Quetiapine

Quetiapine has low D_2 antagonistic properties and low anticholinergic activity. These characteristics must be considered during the switch process, as withdrawal dyskinesia may be more common when switching to quetiapine than with other atypicals, due to reversal of chronic D_2 antagonism(13).
Method four may be suitable in many cases for switches to quetiapine because of the minimal risk of inducing EPSE with quetiapine(13). Rapid switching from haloperidol, risperidone or thioridazine has been generally well tolerated with patients remaining clinically stable(13). However, discontinuation effects of the first antipsychotic should always be considered. Quetiapine should be administered twice daily and slowly up titrated(17).

Risperidone

Switch strategy 3 is recommended for switches to risperidone(17). Due to the alpha-blocking activity of risperidone, orthostatic hypotension can occur, especially during the initial dose titration period. Consequently, medication should be titrated gradually in view of this risk (17). Caution is required with switches involving clozapine, as risperidone can elevate clozapine levels by competitive metabolism via CYP2D6(33).

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References available on request